

CM We claim:

1. A compound of the formula PS

71 (pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z TM (L)A

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(I)

PS and the pharmaceutically acceptable salts thereof wherein:

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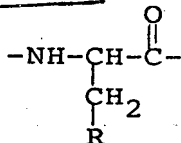
P₁ V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

P₁ W is tyrosyl, phenylalanyl or 3-(1-pentafluorophenyl)-L-alanyl;

a

P₁ X is a D-amino acid residue

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~~70490X~~
(P₁) wherein R is

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P₂ (a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or

25

P₂ (b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydronaphthyl, perhydrobiphenyl, perhydro-2,2-diphenylmethyl and adamantyl;

P₁ Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

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P₁ Z is glycine or $\frac{1}{m}\text{-NH-}\frac{1}{m}\text{R}^1$, wherein

R^1 is lower alkyl, cycloalkyl, fluoro lower alkyl or
 -NH-C(=O)-NH-R^2 wherein
 R^2 is hydrogen or lower alkyl.

2. The compound of Claim 1 wherein V is
 tryptophyl or phenylalanyl; W is tyrosyl; X is
 3-(2-naphthyl)-D-alanyl or 3-(2,4,6-trimethylphenyl)-D-
 alanyl; Y is leucyl or N-methyl-leucyl; and Z is glycine
 amide or ~~polyethylene~~ ^{NHET} amide.

3. The compound of Claim 2 wherein X is
 3-(2-naphthyl)-D-alanyl.

4. The compound of Claim 2 which is (pyro)Glu-
 His-Trp-Ser-Tyr-3-(2-naphthyl)-D-alanyl-Leu-Arg-Pro-
 Gly-NH₂ and the pharmaceutically acceptable acid salts
 thereof.

5. The compound of Claim 3 which is (pyro)Glu-
 His-Trp-Ser-Tyr-3-(2-naphthyl)-D-alanyl-N-methyl-Leu-Arg-
 Pro-Gly-NH₂ and the pharmaceutically acceptable salts
 thereof.

6. The compound of Claim 3 which is (pyro)Glu-His-
 Trp-Ser-Tyr-3-(2-naphthyl)-D-alanyl-Leu-Arg-Pro-NHET and
 the pharmaceutically acceptable salts thereof.

7. The compound of Claim 3 which is (pyro)Glu-His-
 Trp-Ser-Tyr-3-(2-naphthyl)-D-alanyl-N-methyl-Leu-Arg-Pro-
 NHET and the pharmaceutically acceptable salts thereof.

8. The compound of Claim 3 which is (pyro)Glu-His-Phe-Ser-Syr-3-(2-naphthyl)-D-alanyl-Leu-Arg-Pro-Gly-NH₂ and the pharmaceuticly acceptable salts thereof.

5 9. The compound of Claim 2 wherein X is 3-(2,4,6-trimethylphenyl)-D-alanyl.

10 10. The compound of Claim 9 which is (pyro)Glu-His-Trp-Ser-Tyr-3-(2,4,6-trimethylphenyl)-D-alanyl-Leu-Arg-Pro-Gly-NH₂ and the pharmaceutically acceptable salts thereof.

15 11. A method of inhibiting ovulation in a female mammalian subject which method comprises administering to said subject an effective amount of a compound of the formula PS

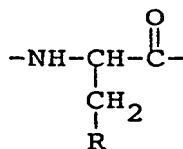
T (pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z TM (I) PS

20 PS or a pharmaceutically acceptable salt thereof wherein:

P₁ V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

25 P₂ W is tyrosyl, phenylalanyl or 3-(1-pentafluorophenyl)-L-alanyl;

a P₃ X is a D-amino acid residue



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(P, FID) wherein R is

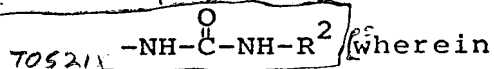
5 P_2 (a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or

10 P_2 (b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydro-naphthyl perhydrobiphenyl, perhydro-2,2-diphenylmethyl and adamantyl;

15 P_1 Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

P_1 Z is glycine or $\frac{1}{m}\text{NH}-\frac{1}{m}\text{R}^1$, wherein

P_1 R^1 is lower alkyl, cycloalkyl, fluoro lower alkyl or



20 P_1 R^2 is hydrogen or lower alkyl, or a pharmaceutical composition containing same.

a ~~12. A pharmaceutical composition for inhibition of~~
~~ovulation in a female mammal comprising~~ ^{an effective amount of} a compound of the
 25 formula P_5

71 (pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z TM (I) P_5

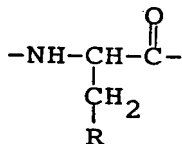
(I)

PS or a pharmaceutically acceptable salt thereof wherein:

P₁ V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-~~L~~-alanyl;

5 P₁ W is tyrosyl, phenylalanyl or 3-(1-pentafluoro-phenyl)-L-alanyl;

a P₁ X is a D-amino acid ^{residue}



~~TO 530 X~~

10 (P₁) wherein R is

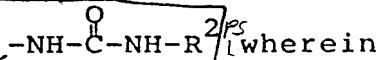
P₂ (a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or

15 P₂ (b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydronaphthyl, perhydrobiphenyl, perhydro-2,2-diphenylmethyl and adamantyl;

20 P₁ Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

P₁ Z is glycine or -NH-CH(R¹)-CO- , wherein

R¹ is lower alkyl, cycloalkyl, fluoro lower alkyl or



P₁ R² is hydrogen or lower alkyl, in admixture with a pharmaceutically acceptable non-toxic carrier.

30 13. A method of treating endometriosis in a female mammalian subject which method comprises administering to

said subject an effective amount of a compound of the formula P_2

5 T_1 (pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z $TM(I) R$

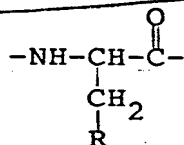
(I)

P_2 or a pharmaceutically acceptable salt thereof wherein:

10 P_1 V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

P_1 W is tyrosyl, phenylalanyl or 3-(1-pentafluorophenyl)-L-alanyl;

a P_1 X is a D-amino acid ^{residue}



T05404
(P_1+10) wherein R is

20 P_2 (a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or

25 P_2 (b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydro-naphthyl, perhydrobiphenyl, perhydro-2,2-diphenylmethyl and adamantyl;

P_1 Y is leucyl, isoleucyl, nor-leucyl or N-methyl-

leucyl;

f_1 Z is glycine or NH-R^1 , wherein

f_1 R^1 is lower alkyl, cycloalkyl, fluoro lower alkyl or

~~70650X~~ $\text{NH}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{NH-R}^2$ wherein

f_1 R^2 is hydrogen or lower alkyl, or a pharmaceutical composition containing same.

14. A pharmaceutical composition for treatment of endometriosis in a female mammal comprising a compound of the formula

(pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z

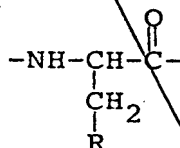
(I).

or a pharmaceutically acceptable salt thereof wherein:

V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

W is tyrosyl, phenylalanyl or 3-(1-pentafluorophenyl)-L-alanyl;

X is a D-amino acid



wherein R is

(a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl

groups; or

(b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydro-naphthyl, perhydrobiphenyl, perhydro-2,2-diphenylmethyl and adamantyl;

Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

Z is glycine or -NH-R^1 , wherein

R^1 is lower alkyl, cycloalkyl, fluoro lower alkyl or -NH-C(=O)-NH-R^2 wherein

R^2 is hydrogen or lower alkyl, in addition with a pharmaceutically acceptable, non-toxic carrier.

14.
15. A method of treating benign prostatic hypertrophy in a male mammalian subject which method comprises administering to said subject an effective amount of a compound of the formula PS

TI (pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z TM (I) PS

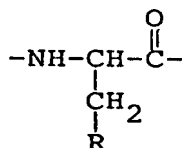
(I)

PS or a pharmaceutically acceptable salt thereof wherein:

P₁ V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

P₁ W is tyrosyl, phenylalanyl or 3-(1-pentafluorophenyl)-L-alanyl;

P₁ X is a D-amino acid residue

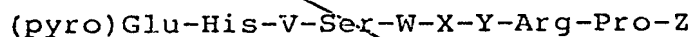


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wherein R is

- 5 R_2 (a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or
- 10 R_2 (b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydro-naphthyl, perhydrobiphenyl, perhydro-2,2-diphenylmethyl and adamantyl;
- 15 Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;
- Z is glycine or $\text{NH}-\text{R}^1$, wherein
- R^1 is lower alkyl, cycloalkyl, fluoro lower alkyl or
- 20 $\text{NH}-\text{C}(=\text{O})-\text{NH}-\text{R}^2$ wherein
- R^2 is hydrogen or lower alkyl, or a pharmaceutical composition containing same.

25 16. A pharmaceutical composition for treatment of benign prostatic hypertrophy in a male mammal comprising a compound of the formula



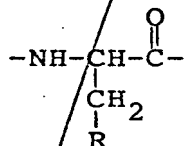
(I)

or a pharmaceutically acceptable salt thereof wherein:

V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

W is tyrosyl, phenylalanyl or 3-(1-pentafluorophenyl)-L-alanyl;

X is a D-amino acid



wherein R is

(a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or

(b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydronaphthyl, perhydrobiphenyl, perhydro-2,2-diphenylmethyl and adamantyl;

Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

Z is glycinamide or -NH-R^1 , wherein

R^1 is lower alkyl, cycloalkyl, fluoro lower alkyl or -NH-C(=O)-NH-R^2 wherein

R^2 is hydrogen or lower alkyl, in admixture with a pharmaceutically acceptable, non-toxic carrier.

~~15.~~
~~17.~~ A method of inhibiting spermatogenesis in a male mammalian subject which method comprises

administering to said subject an effective amount of a compound of the formula PS

71 (pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z 7M (2) PS

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(I)

PS or a pharmaceutically acceptable salt thereof wherein:

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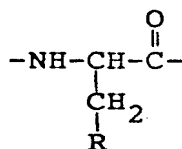
P₁ V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

P₁ W is tyrosyl, phenylalanyl or 3-(1-pentafluorophenyl)-L-alanyl;

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P₁ X is a D-amino acid^{residue}

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P₁ + 10

wherein R is

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P₂ (a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or

25

P₂ (b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydronaphthyl, perhydrobiphenyl, perhydro-2,2-diphenylmethyl and adamantyl;

Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

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P₁ Z is glycine or $\frac{1}{n_1}\text{NH}-\text{R}^1$, wherein

R^1 is lower alkyl, cycloalkyl, fluoro lower alkyl or
-NH-C(=O)-NH-R² wherein

R^2 is hydrogen or lower alkyl, or a pharmaceutical composition containing same.

18. A pharmaceutical composition for inhibiting spermatogenesis in a male mammal comprising a compound of the formula

(pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z

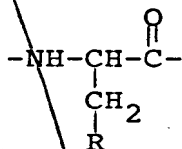
(I)

and the pharmaceutically acceptable salts thereof wherein:

V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

W is tyrosyl, phenylalanyl or 3-(1-pentafluorophenyl)-L-alanyl;

X is a D-amino acid



wherein R is

(a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or

(b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydro-

naphthyl, perhydrobiphenyl, perhydro-2,2-diphenylmethyl and adamantyl;

Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

Z is glycineamide or $-\text{NH}-\text{R}^1$, wherein

R^1 is lower alkyl, cycloalkyl, fluoro lower alkyl or $-\text{NH}-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\text{NH}-\text{R}^2$ wherein

R^2 is hydrogen or lower alkyl, in admixture with a pharmaceutically acceptable, non-toxic carrier.

19. A process for the preparation of a compound of the formula

(pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z

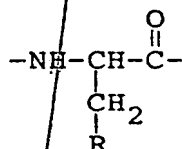
(I)

and the pharmaceutically acceptable salts thereof wherein:

V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

W is tyrosyl, phenylalanyl or 3-(1-pentafluorophenyl)-L-alanyl;

X is a D-amino acid



wherein R is

(a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenyl, benzhydryl and phenyl

substituted with three or more straight chain lower alkyl groups; or

(b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydro-naphthyl, perhydrobiphenyl, perhydro-2,2-diphenylmethyl and adamantyl;

Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

Z is glycine or -NH-R^1 , wherein

R^1 is lower alkyl, cycloalkyl, fluoro lower alkyl or -NH-C(=O)-NH-R^2 wherein

R^2 is hydrogen or lower alkyl, which process comprises:

(i) removing protecting groups and optionally covalently bound solid support from a protected polypeptide to afford a compound of Formula (I) or a salt thereof, and optionally

(ii) converting a compound of Formula (I) to a pharmaceutically acceptable salt,

(iii) converting a salt of a compound of Formula (I) to a pharmaceutically acceptable salt, or

(iv) decomposing a salt of a compound of Formula (I) to a free polypeptide of Formula (I).